Hot News

Low Performance of Protease Inhibitor Monotherapy in Comparison with Standard Triple Regimens

Albeit that the introduction of HAART more than one decade ago represented a hallmark in HIV infection and remains the gold standard, simpler drug regimens are being sought in an attempt to reduce side effects and enhance compliance. Given their characteristic pharmacokinetics, ritonavir-boosted protease inhibitors (PI) in monotherapy have recently been regarded as a potential alternative option to standard triple therapy, at least in particular circumstances (Swindell, et al. JAMA. 2006;296:806-14).

Two studies have recently reported safety and efficacy results using lopinavir/ritonavir (LPV/r) as monotherapy, either in drug-naive subjects (Delfraissy, et al. AIDS. 2008;22:385-93) or as simplification strategy in patients with complete viral suppression under a triple regimen (Pulido, et al. AIDS. 2008;22: F1-9). An in-depth analysis of both studies brings the reader to the conclusion that either as first-line (the MONARK study) or as simplification (the OK04 study), PI monotherapy underperformed the triple regimens (Table 1).

	LPV/r + 2 NRTI	LPV/r alone	p
Monark	53	83	
ITT	75%	67%	0.34
OT	98%	84%	0.03
OK04	98	100	
ITT	90%	85%	0.31
OT	96.7%	88.5%	0.049

LPV/r: lopinavir boosted with ritonavir; NRTI: nucleoside reverse transcriptase inhibitors; ITT: intent-to-treat; OT: on therapy.

The MONARK study compared LPV/r plus Combivir® (zidovudine plus lamivudine) versus LPV/r as monotherapy as initial treatment of HIV infection. Although differences at 48 weeks between the two arms could not be recognized when comparing results in an intent-to-treat basis, a significant superiority of the triple arm in comparison with the PI monotherapy was seen examining only patients on therapy (98 vs. 80%). The incidence of side effects was not significantly different in both treatment arms, questioning the advantage of monotherapy, aside from less pills.

The OK04 study compared LPV/r as monotherapy versus LPV/r combined with two nucleoside analogs, establishing as primary endpoint the non-inferiority of the simplification treatment in terms of virologic response (< 50 HIV RNA copies/ml) at 48 weeks. Although, in an intention-to-treat basis, differences in virologic response did not reach statistical significance, a trend towards superiority of the triple-therapy arm compared to monotherapy was noticed (88.2 vs. 82.5%, respectively). Moreover, considering only subjects on therapy, triple therapy was significantly superior to PI monotherapy (96.7 vs. 88.5%, respectively). It is remarkable that according to the OK04 study design, four patients with therapeutic failure in the monotherapy arm were re-induced with two nucleoside analogs and, as they reached viral suppression, were not considered as therapeutic failures. The use of non-parametric statistical tests in this study also raises doubts about whether those differences would be even more significant with a more appropriate analysis.

Although simple antiretroviral regimens are desirable, the current evidence does not support moving off triple-drug therapy, using only drugs with a high genetic barrier to resistance such as ritonavir-boosted PI. In the case of LPV/r, frequent side effects, such as dyslipidemia, insulin resistance, diarrhea and the twice-daily dosing, make other drugs more attractive as simplification therapy.

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Protective Effect of Nevirapine on Liver Fibrosis Progression in HIV/HCV Coinfected Patients

An association between exposure to nevirapine (NVP) and reduced liver fibrosis progression in HIV/HCV coinfected patients was recently reported by Spanish investigators (Berenguer, et al. Clin Infect Dis. 2008;46:137-43). The authors examined 201 coinfected patients who underwent a liver biopsy as part of a pretreatment assessment of chronic hepatitis C. As in prior studies that had examined correlates of exposure to antiretroviral therapy and hepatic damage, liver fibrosis progression was calculated after dividing the fibrosis stage score by the estimated duration of HCV infection (Benhamou, et al. Hepatology. 1999;30:1054-8).

It is widely accepted that the liver toxicity of antiretroviral drugs could enhance liver fibrosis in HIV/HCV coinfected patients (Soriano, et al. AIDS. 2008;21:1-13). On the other hand, HAART-related immune restora-

tion could lessen HCV-associated liver damage (Qurishi, et al. Lancet. 2003;362:1708-13). In this regard, a particular beneficial effect of protease inhibitors has been claimed by some authors (Benhamou, et al. Hepatology. 2001;34:283-7). Moreover, along with the benefit of protease inhibitors, one study claimed a harmful impact of NVP on liver fibrosis progression (Pineda, et al. AIDS. 2004;18:767-74). As with the Berenguer study, this was a cross-sectional analysis, this time assessing 152 HIV/HCV coinfected patients who underwent a liver biopsy.

Since transversal observations mainly permit obtaining information about prevalence, some biases inherent to this design may distort any estimation of the effects of single antiretroviral drugs on liver fibrosis progression. Understanding the mechanisms and effects of biases will help to interpret an eventual protective or harmful effect of NVP on liver fibrosis progression.

In both the Berenguer and Macias studies, the examined HIV/HCV coinfected patients were those who filled the criteria to be treated for chronic hepatitis C with pegylated interferon plus ribavirin. For this reason they had a liver biopsy, which permitted to obtain information on liver fibrosis staging. It should be noted that the liver biopsy was mainly requested from patients with good CD4 counts, adherent to HAART, stable undetectable plasma HIV RNA, etc. and might not represent the whole population of HIV/HCV coinfected patients. This absence of representativeness could under or overestimate the appreciation of any effect of single antiretroviral agents.

As an example, to be candidate for pegylated interferon plus ribavirin and therefore justify a liver biopsy, patients should have no contraindication for anti-HCV therapy. Accordingly, patients with decompensated liver cirrhosis would be excluded. This subset of patients would systematically be excluded, leading to an underestimation of the effect of antiretroviral agents on liver fibrosis. This effect is known as the "selective survival effect".

Another source of bias is represented by the "healthy patient effect". Subjects who died before the inclusion period might be more often exposed to specific drugs. Of course, selection of healthy patients might underestimate a harmful impact of single antiretroviral agents on liver fibrosis progression.

To improve validity and diminish the effect of selection biases, random selection of the whole population of HIV/HCV coinfected patients exposed to antiretroviral agents should be considered. In this scenario, a liver biopsy could no longer be considered as the most appropriate diagnostic tool for obvious ethical considerations. Noninvasive techniques (e.g. FibroScan, FibroTest, etc.) may represent suitable tools to assess liver fibrosis progression longitudinally in coinfected patients on prolonged antiretroviral therapy. Since these techniques are not the gold standard for staging liver fibrosis, another bias, this time called the "information bias", may arise (Grimes, et al. Lancet. 2002;359:248-52). It is the bias of considering liver fibrosis when not present and *vice versa*.

In summary, in HIV/HCV coinfected patients under NVP-based regimens and tolerating the medication well, a beneficial effect of NVP on liver fibrosis progression may be recognized. This effect may result from the immune restoration associated to HAART rather than from any specific effect of single antiretroviral agents.

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Warning on Hepatotoxicity of Darunavir

The U.S. Food and Drug Administration (FDA) has, in March 2008, released a warning concerning the risk of hepatotoxicity using darunavir boosted with ritonavir. Although significant liver enzyme elevations had already been seen during the clinical development of darunavir, in which 3,063 patients received the drug, hepatitis was reported in only 0.5% of cases. As expected, subjects with preexisting liver dysfunction, including chronic hepatitis B or C, were at increased risk of liver function abnormalities following treatment with darunavir-based regimens.

Post-marketing cases of liver injury, including some fatalities, have recently been reported. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications, having comorbidities including hepatitis B or C coinfection, and/or developing an immune reconstitution syndrome. On the basis of this information, the FDA recommends appropriate laboratory testing prior to initiating therapy with darunavir, and close monitoring of liver enzymes during treatment. Increased AST/ALT levels should be identified early, especially in patients with underlying chronic hepatitis or cirrhosis, or in patients who have pretreatment elevations of transaminases, especially during the first several months of darunavir/ritonavir treatment. If there is evidence of new or worsening liver dysfunction, interruption or discontinuation of treatment must be considered.

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